



Year: 2012

A pooled analysis of sequential therapies with sorafenib and sunitinib in metastatic renal cell carcinoma

Stenner, Frank ; Chastonay, Rahel ; Liewen, Heike ; Haile, Sarah R ; Cathomas, Richard ; Rothermundt, Christian ; Siciliano, Raffaele D ; Stoll, Susanna ; Knuth, Alexander ; Buchler, Tomas ; Porta, Camillo ; Renner, Christoph ; Samaras, Panagiotis

Abstract: **OBJECTIVE:** To evaluate the optimal sequence for the receptor tyrosine kinase inhibitors (rTKIs) sorafenib and sunitinib in metastatic renal cell cancer. **METHODS:** We performed a retrospective analysis of patients who had received sequential therapy with both rTKIs and integrated these results into a pooled analysis of available data from other publications. Differences in median progression-free survival (PFS) for first- (PFS1) and second-line treatment (PFS2), and for the combined PFS (PFS1 plus PFS2) were examined using weighted linear regression. **RESULTS:** In the pooled analysis encompassing 853 patients, the median combined PFS for first-line sunitinib and 2nd-line sorafenib (SuSo) was 12.1 months compared with 15.4 months for the reverse sequence (SoSu; 95% CI for difference 1.45-5.12, $p = 0.0013$). Regarding first-line treatment, no significant difference in PFS1 was noted regardless of which drug was initially used (0.62 months average increase on sorafenib, 95% CI for difference -1.01 to 2.26, $p = 0.43$). In second-line treatment, sunitinib showed a significantly longer PFS2 than sorafenib (average increase 2.66 months, 95% CI 1.02-4.3, $p = 0.003$). **CONCLUSION:** The SoSu sequence translates into a longer combined PFS compared to the SuSo sequence. Predominantly the superiority of sunitinib regarding PFS2 contributed to the longer combined PFS in sequential use.

DOI: <https://doi.org/10.1159/000338001>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-69448>

Journal Article

Published Version

Originally published at:

Stenner, Frank; Chastonay, Rahel; Liewen, Heike; Haile, Sarah R; Cathomas, Richard; Rothermundt, Christian; Siciliano, Raffaele D; Stoll, Susanna; Knuth, Alexander; Buchler, Tomas; Porta, Camillo; Renner, Christoph; Samaras, Panagiotis (2012). A pooled analysis of sequential therapies with sorafenib and sunitinib in metastatic renal cell carcinoma. *Oncology*, 82(6):333-340.

DOI: <https://doi.org/10.1159/000338001>

A Pooled Analysis of Sequential Therapies with Sorafenib and Sunitinib in Metastatic Renal Cell Carcinoma

Frank Stenner^a Rahel Chastonay^a Heike Liewen^a Sarah R. Haile^b Richard Cathomas^e
Christian Rothermundt^d Raffaele D. Siciliano^c Susanna Stoll^f Alexander Knuth^a
Tomas Buchler^g Camillo Porta^h Christoph Renner^a Panagiotis Samaras^a

^aDepartment of Medical Oncology, University Hospital Zurich, and ^bDivision of Biostatistics, Institute of Social and Preventive Medicine, University of Zurich, and ^cTriemli City Hospital, Zurich, ^dCantonal Hospital St. Gallen, St. Gallen, ^eCantonal Hospital Graubünden, Chur, and ^fCantonal Hospital Aarau, Aarau, Switzerland; ^gDepartment of Oncology and First Faculty of Medicine, Thomayer University Hospital and Charles University, Prague, Czech Republic; ^hMedical Oncology, IRCCS, San Matteo University Hospital Foundation, Pavia, Italy

Key Words

Renal cell carcinoma • Sorafenib • Sunitinib • Treatment regimens • Tyrosine kinase inhibitors

Abstract

Objective: To evaluate the optimal sequence for the receptor tyrosine kinase inhibitors (rTKIs) sorafenib and sunitinib in metastatic renal cell cancer. **Methods:** We performed a retrospective analysis of patients who had received sequential therapy with both rTKIs and integrated these results into a pooled analysis of available data from other publications. Differences in median progression-free survival (PFS) for first- (PFS1) and second-line treatment (PFS2), and for the combined PFS (PFS1 plus PFS2) were examined using weighted linear regression. **Results:** In the pooled analysis encompassing 853 patients, the median combined PFS for first-line sunitinib and 2nd-line sorafenib (SuSo) was 12.1 months compared with 15.4 months for the reverse sequence (SoSu; 95% CI for difference 1.45–5.12, $p = 0.0013$). Regarding first-line treatment, no significant difference in PFS1 was noted

regardless of which drug was initially used (0.62 months average increase on sorafenib, 95% CI for difference –1.01 to 2.26, $p = 0.43$). In second-line treatment, sunitinib showed a significantly longer PFS2 than sorafenib (average increase 2.66 months, 95% CI 1.02–4.3, $p = 0.003$). **Conclusion:** The SoSu sequence translates into a longer combined PFS compared to the SuSo sequence. Predominantly the superiority of sunitinib regarding PFS2 contributed to the longer combined PFS in sequential use.

Copyright © 2012 S. Karger AG, Basel

Introduction

Renal cell carcinoma (RCC) is one of the ten most common cancers worldwide, being diagnosed predominantly in more developed countries [1]. Until the advent

F.S. and R.C. contributed equally to this study. P.S. and C.R. share senior authorship.

of ‘targeted therapies’, no promising treatment options were available for metastatic RCC (mRCC) and the disease progressed most often rapidly. Receptor tyrosine kinase inhibitors (rTKIs) have significantly altered the clinical course of mRCC. As of today, three rTKIs, namely sorafenib, sunitinib and pazopanib, have been approved by regulatory authorities and are used routinely [2–4]. Next-generation rTKIs like tivozanib are being evaluated, while axitinib is on the brink of entering the clinic. Besides rTKIs, interferon α in combination with the anti-VEGF antibody bevacizumab and the mTOR inhibitors temsirolimus and everolimus are commonly used for mRCC therapy [5–7]. Sunitinib has emerged as the most frequently applied drug in first-line therapy, while sorafenib has been the first rTKI to be approved for treatment of mRCC after first-line cytokine treatment. After introduction of these two drugs into the clinic, control rates regarding progression and overall survival (OS) improved markedly [2, 3].

Based on the RECORD-1 trial, second-line therapy with everolimus after failure or intolerance to an rTKI is a reasonable treatment strategy [7]. This concept has been challenged by several reports evaluating the use of sorafenib and sunitinib in a sequential manner [8–20]. The majority of these trials found no evidence for cross-resistance, and thus prolonged exposure to rTKIs by sequential treatment, at least for a significant subset of patients, may be possible.

To address this question further, we performed a pooled analysis of the available published data as well as of our own experience in patients treated at five Swiss centers.

Patients and Methods

The records from patients with mRCC who were treated either with sunitinib as first-line treatment and sorafenib as second-line treatment (SuSo) or the reverse sequence (SoSu) at five Swiss centers were retrospectively reviewed and assessed with regard to progression-free survival (PFS). Data acquisition and analysis was approved by the local ethics committee (reference ethics committee No. KEK-ZH: 2009-0070/0). Response was assessed on imaging data available by using the revised Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) [21]. In patients without available imaging data, response was assessed by analyzing the radiographic reports or the data entries of the attending physicians in the patient charts. PFS1 was defined as time from start of the first rTKI to the time of first progression, and PFS2 as time from start of the second rTKI to the time of second progression or death by any cause. Combined PFS was defined as the sum of PFS1 and PFS2 for the complete rTKI-sequence efficacy. The treatment-free interval between the sequential rTKI therapies was not included.

Data for the pooled analysis were collected by searching PubMed, Embase and the Cochrane Library. In addition, we checked relevant references from seminal articles or reviews for studies reported at international meetings. The search term used for the PubMed search was: ‘Sorafenib [All Fields] AND Sunitinib [All Fields] AND (Sequential [All Fields] OR Renal [All Fields] OR (Sequential [All Fields] AND Renal [All Fields]))’. The corresponding search term for Embase was: ‘sorafenib’:ab,ti AND ‘sunitinib’:ab,ti AND [‘sequential’/exp OR ‘renal’/exp OR (‘sequential’ AND ‘renal’/exp)]. The cutoff date was May 15, 2011. Data regarding basic patient characteristics, treatment sequencing and PFS for each line of therapy, OS, response and tumor control rate were registered if available. We integrated all data including our own into a pooled analysis and examined differences in median PFS using weighted linear regression. The analysis was performed with all reported data available and repeated as sensitivity re-analysis after exclusion of the following studies:

- studies in which subsets of patients had reportedly received anti-angiogenic compounds or chemotherapy before starting the sequential TKI treatment.
- studies in which the reason for treatment discontinuation was not identifiable as PFS.
- studies in which treatment discontinuation due to toxicity or intolerance was included into the definition of progression.

Patients who had received prior cytokine treatment were allowed in the sensitivity re-analysis. This sensitivity re-analysis was performed to reduce bias due to heterogeneity of the study designs and the patient cohorts.

All analysis was performed in the R programming language [22, 23].

Results

Twenty-one Swiss patients were identified with sufficient data available regarding combined PFS and added to the pooled analysis. The individual treatment decisions regarding the treatment sequence were driven by the registration status of the two drugs. Patients were initially treated with sorafenib, the first drug registered for the use in mRCC, and when Sutent became available all subsequent patients were treated with the latter drug. The survival data of these patients are summarized in table 1. After in-depth review of the literature, 19 trials have been identified reporting on sequential treatment with sunitinib and sorafenib. After exclusion of duplicate reports, studies having included other drugs in the sequence like mTOR inhibitors and trials with insufficient reported data, 12 published studies with sufficient data available regarding combined PFS and our own data could be included into the pooled analysis (fig. 1). Eleven studies were retrospective analyses, and 2 were prospective trials. Three studies had included patients with preceding anti-angiogenic or chemotherapy treatment. Overall, 853 patients had been treated sequentially and

Table 1. Trials included with sequential rTKI treatment

Study	Design	Study arms n	Sequence	Patients, n		Median PFS, months		Median age years	Clear-cell %	Patients, %	
				(n = 455)	(n = 398)	PFS1	PFS2			prior cytokines	prior chemo-/ anti-angiotherapy
Tamaskar et al. [8]	Retro.	2	So→Su	4	–	4.4*	7.7*	62 ¹	93 ¹	0	25
			Su→So	–	5	8.6*	5.9*			0	60
Richter et al. [9]	Retro.	2	So→Su	5	–	7.9*	9.8*	NR	NR	NR	NR
			Su→So	–	5	8.5*	8.9*			NR	NR
Zimmermann et al. [10]	Retro.	1	So→Su	22	–	11.6	5	61.5	100	54.5	0
Choueiri et al. [12]	Retro.	2	So→Su	31	–	8.6 [†]	5.8 [†]	NR	NR	NR	NR
			Su→So	–	7	8.1 [†]	2.6 [†]			NR	NR
Heuer et al. [13]	Retro.	1	So→Su	44	–	9.2	5.7	NR	84	65	0
Dudek et al. [14]	Retro.	2	So→Su	29	–	5.1	13.1	62	86	55	0
			Su→So	–	20	5.8	2.8			80	0
Di Lorenzo et al. [15]	Prosp.	1	Su→So	–	52	5.6	3.7	60	87	21	0
Sablin et al. [16]	Retro.	2	So→Su	68	–	6	6.5	60	82	50	18
			Su→So	–	22	5.1	4			41	49
Porta et al. [32]	Retro.	2	So→Su	90	–	8.39	7.89	58	84	54 ¹	NR
			Su→So	–	99	7.79	4.24			87	NR
Garcia et al. [17]	Prosp.	1	Su→So	–	27	13.1	4.4	64	100	37	30
Buchler et al. [18]	Retro.	2	So→Su	122	–	7.82	8.64	60	100	94	NR
			Su→So	–	138	7.23	5.68			85	NR
Herrmann et al. [19]	Retro.	2	So→Su	29	–	9.3	3.4	64 ¹	72 ¹	0	0
			Su→So	–	13	9.8	3.8			0	0
Own patients (this study)	Retro.	2	So→Su	10	–	5.39	6.01	57.1	80	30	0
			Su→So	–	11	12.71	3.71			0	0

Mean values are marked with an asterisk, and data reported as treatment duration with a dagger. Retro. = Retrospective; Prosp. = prospective; NR = not reported. ¹ Reported for the whole patient population.

were eligible for analysis (398 patients received SuSo and 455 patients SoSu), and for 470 (55%) of them, the complete source data were available [247 (62%) patients with SuSo and 223 (49%) patients with SoSu]. The details of the studies included are depicted in table 1. A longer combined PFS for the SoSu sequence compared to SuSo was found in the pooled analysis (median combined PFS on SuSo was 12.1 months compared with 15.4 months on SoSu, 95% CI for difference 1.45–5.12, $p = 0.0013$; fig. 2). No statistically significant difference in the time to first progression (PFS1) was noted regardless of which drug was initially used (median PFS1 was on average 0.62 months longer on SoSu, 95% CI for difference –1.01 to 2.26, $p = 0.43$). In second-line treatment, sunitinib showed a significantly longer PFS2 than sorafenib (average increase of 2.66 months, 95% CI for difference 1.02–4.3, $p = 0.003$; (fig. 3).

These results could also be confirmed by a more homogenous sensitivity re-analysis after exclusion of 5 studies (Tamaskar et al. [8], Sablin et al. [16], Garcia et al. [17], Dudek et al. [14] and Choueiri et al. [12]), which either reported substantial pre-treatment of the patients with anti-angiogenic compounds and chemotherapy, or used varying definitions for progression. Of overall 640 patients with source data available, 470 (73%) were still included into this re-analysis. The median combined PFS was 12.1 months for SuSo compared with 15.9 months for SoSu (95% CI for difference 2.08–5.54, $p = 0.0005$; fig. 4).

Neither patient age, gender distribution nor study design (retrospective vs. prospective) was statistically significantly associated with PFS in either line. The impact of sequential therapy on OS and treatment-associated toxicities could not be assessed due to insufficient data reported by the studies.

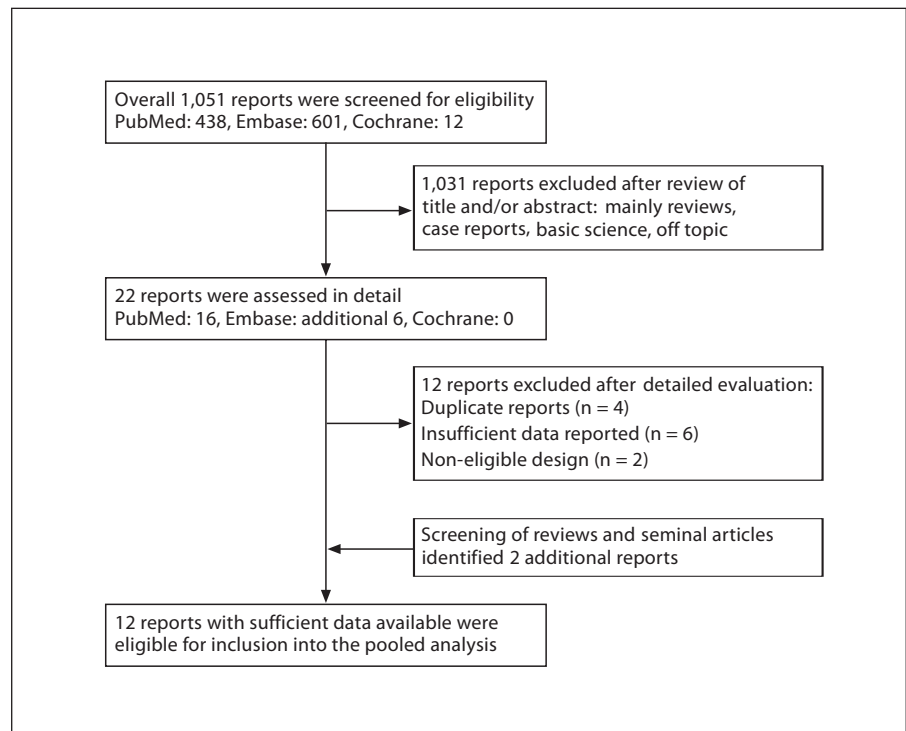


Fig. 1. Flow chart of data acquisition.

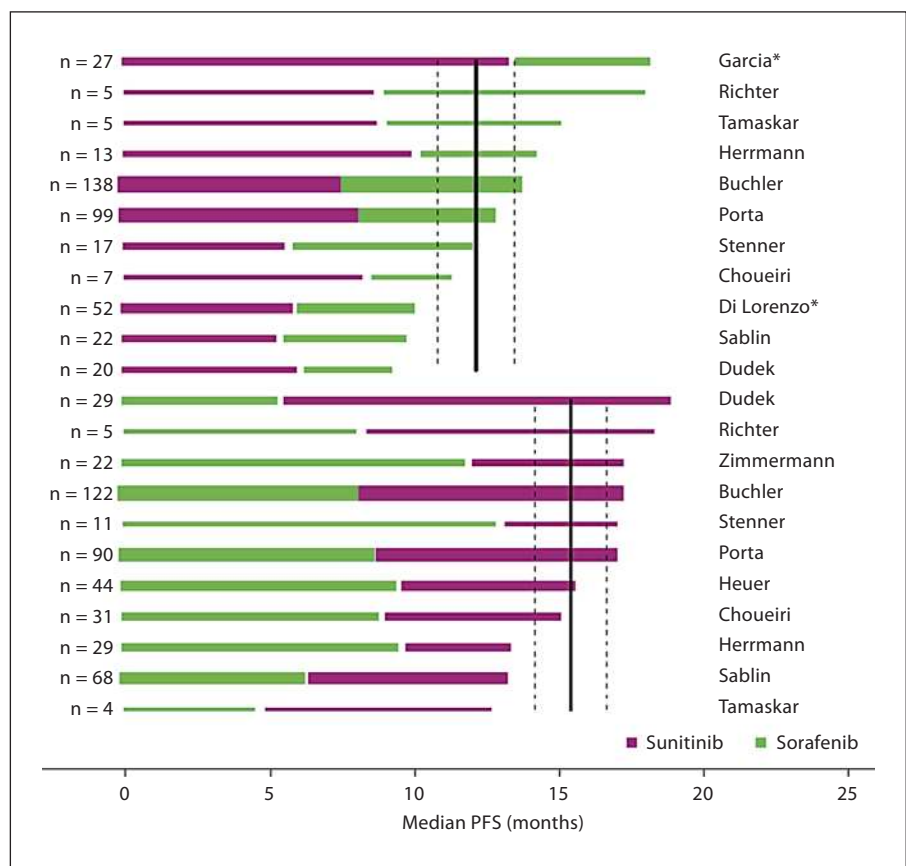


Fig. 2. Pooled analysis of the median PFS from available data in the literature. Combined PFS on SuSo was 12.1 months compared with 15.4 months on SoSu (95% CI for difference 1.45–5.12; $p = 0.0013$). The relative proportion of patients from each study contributing to the total analysis is represented by the varying thickness of the bars. Prospective studies are marked with an asterisk.

Fig. 3. Pooled PFS at first- (a) and second-line treatment (b) of available trials. Median PFS1 was on average 0.62 months longer on sorafenib compared with sunitinib (95% CI for difference -1.01 to 2.26, $p = 0.43$). **b** Sunitinib showed a significantly longer PFS than sorafenib regarding median PFS2 (average increase of 2.66 months, 95% CI for difference 1.02–4.3, $p = 0.003$).

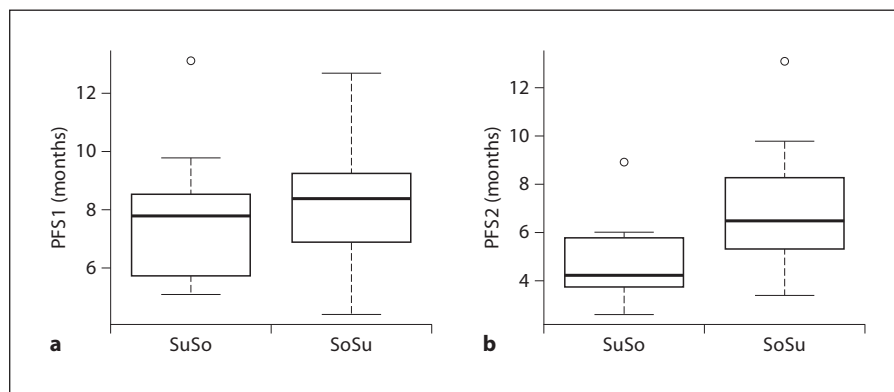
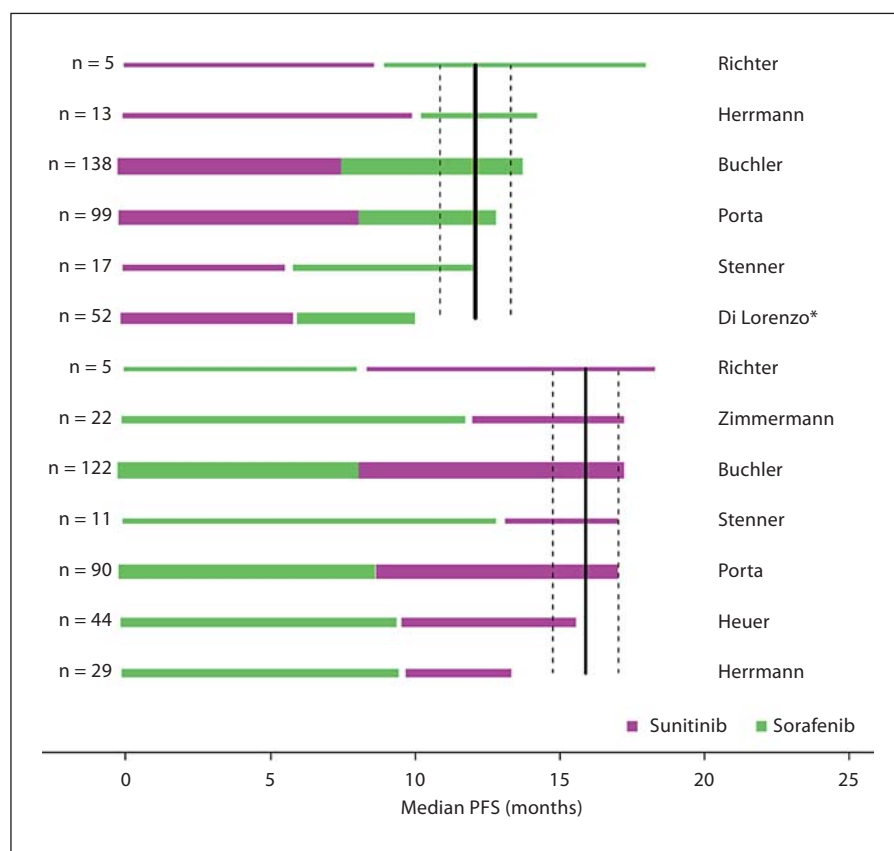


Fig. 4. Sensitivity re-analysis of the median PFS after exclusion of 5 studies. Median combined PFS on SuSo was 12.1 months compared with 15.9 months on SoSu (95% CI for difference 2.08–5.54, $p = 0.0005$). The relative proportion of patients from each study contributing to the total analysis is represented by the varying thickness of the bars. Prospective studies are marked with an asterisk.



Color version available online

Discussion

A longer combined PFS for SoSu compared to SuSo was observed in this pooled analysis. The gain in combined PFS was mainly achieved by a prolonged PFS2 with sunitinib when given in second line compared to sorafenib, with an average increase in median PFS2 of 2.7 months. While some of the included studies have hinted

towards a superiority of the SoSu versus the SuSo sequence, others have found no difference regarding PFS. This discrepancy may be explained by the definition of combined PFS by the respective groups. We have analyzed the PFS period for every treatment line separately and calculated the sum of PFS1 and PFS2 without considering the treatment-free interval. One large study defining overall PFS from the start of the first rTKI to progres-

sion on the second rTKI including the treatment-free interval reported similar efficacy for both treatment sequences [18]. However, when PFS periods are analyzed separately without considering the treatment-free interval, sunitinib achieves a prolonged PFS in second-line treatment compared with sorafenib (8.64 vs. 5.68 months; data from Buchler [hitherto unpubl. results]).

The impact of the treatment-free interval on total PFS may be explained by a more pronounced drug carryover effect after cessation of sunitinib compared to sorafenib. Another explanation may be that after failure of first-line sorafenib patients were earlier willing or fit to receive second-line treatment due to less adverse effects of the drug. Further, the quality of the progression, slow progression versus fast progression, single site versus multiple sites, or more or less life-threatening situation, could influence the physician's decision to start second-line therapy. We came to the conclusion that the duration of the pause between therapies cannot be addressed adequately in a pooled analysis. Thus, we omitted the interval and compared active treatment times of sequential therapies only. OS could not be assessed within our pooled analysis due to insufficient data reported in the published studies. However, in a recently published analysis of the Swedish Health Care registry, median time to death was reported to be superior for the SoSu sequence compared to the SuSo sequence [24].

The AXIS study is the first prospective phase III study showing a benefit for sequential rTKI therapy. In a subgroup analysis, axitinib compared favorably to sorafenib in second-line treatment after failure of first-line sunitinib treatment. The difference was only modest but statistically significant (4.8 months for axitinib vs. 3.4 months for sorafenib, $p = 0.01$). The result highlights the fact that after a potent VEGFR TKI the activity of the second-line VEGFR rTKI is markedly reduced but still active in many patients [25].

Two options based on prospective trial data have now been established for patients that have failed first-line treatment with sunitinib: changing the mode of action by switching to everolimus or maintaining VEGFR inhibition by using axitinib. The fact that the RECORD-1 study had no active control arm and the AXIS study compared one rTKI versus another (sorafenib vs. axitinib) allows no direct comparison of the two strategies yet. Despite the lack of prospective data, several retrospective analyses indicate that both treatment strategies yield nearly equivalent results [26, 27]. Noteworthy, recent data regarding efficacy of further lines of treatment have been published. A PFS of 5.5 months for third-line rTKI treatment after

initial rTKI and second-line everolimus, and a PFS of 4 months for third-line everolimus after first- and second-line rTKIs have been reported [28, 29]. Altogether, the most important factor for the outcome of a patient seems to be an adequate performance status for receiving sequential therapy at all [26, 30].

The majority of reported studies on rTKI sequencing included in this pooled analysis show limited or incomplete cross-resistance of sunitinib and sorafenib. This makes meaningful responses in second-line therapy likely and continuation of rTKI treatment after first-line rTKI reasonable. The value of sunitinib as second-line treatment has also been suggested by the analysis of the final results of the AVOREN trial. Patients treated sequentially with bevacizumab and interferon, followed by sunitinib, had an unparalleled OS of >43 months [31]. It has to be taken into account that patients treated in this study appear to be highly selected, as the control group receiving placebo had also an extraordinary long median OS.

Our pooled analysis supports sequential treatment of sorafenib and sunitinib. The main limitation of this analysis is its retrospective and heterogeneous nature. Furthermore, there could be case selection and treatment bias. Response assessment has been done in some cases by interpreting data entries in patient charts rather than by imaging analysis, which may have contributed to an estimator bias. On the other hand, a pooled analysis of a larger patient cohort may overcome drawbacks of small studies underpowered to detect significant differences, as observed in our own patient collective. In addition, we had access to the source data of the two largest reports. Thus, the analysis was rather based on patient than on summary data.

In conclusion, the results presented herein seem to confirm that both rTKIs used sequentially result in a longer PFS compared to single rTKI treatment. They indicate that sorafenib and sunitinib do not display relevant cross-resistance. The therapeutic SoSu sequence translates into a longer combined PFS in comparison to SuSo. This pooled analysis may help clinicians in choosing a treatment strategy for their patients, but the results from the prospective SWITCH trial (ClinicalTrials.gov identifier: NCT00732914) have to be awaited before definitive conclusions can be drawn on sequential treatment with sunitinib and sorafenib.

Disclosure Statement

The authors declare the following potential conflicts of interests: Dr. F. Stenner has served as a consultant for Bayer and Pfizer. He received honoraria from Bayer, Pfizer, Roche, GSK and Novartis. Dr. C. Rothermundt has received honoraria from Bayer and Novartis. Prof. C. Renner has served as consultant for Pfizer. Dr. P. Samaras has been consultant for Bayer, and has received honoraria from Roche and Bayer. Dr. R. Cathomas has served as con-

sultant for Pfizer. Prof. C. Porta has consultancy and advisory role for and received honoraria from Bayer, Pfizer, Hoffman La Roche, GSK and Novartis. In addition, he received research funding from Bayer and Novartis. Dr. T. Buchler has received honoraria for lectures from Bayer and Roche. Dr. H. Liewen indicated that she has no potential conflicts of interest, but she is the spouse of Dr. Stenner. All other authors have indicated that they have nothing to disclose.

References

- Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D: Global cancer statistics. *CA Cancer J Clin* 2011;61:69–90.
- Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, Negrier S, Chevreau C, Solska E, Desai AA, Rolland F, Demkow T, Hutson TE, Gore M, Freeman S, Schwartz B, Shan M, Simantov R, Bukowski RM: Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007;356:125–134.
- Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, Negrier S, Szczylik C, Pili R, Bjarnason GA, Garcia-del-Muro X, Sosman JA, Solska E, Wilding G, Thompson JA, Kim ST, Chen I, Huang X, Figlin RA: Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2009;27:3584–3590.
- Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, Barrios CH, Salman P, Gladkov OA, Kavina A, Zarba JJ, Chen M, McCann L, Pandite L, Roychowdhury DF, Hawkins RE: Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol* 2010;28:1061–1068.
- Escudier B, Pluzanska A, Koralewski P, Ravaud A, Bracarda S, Szczylik C, Chevreau C, Filipek M, Melichar B, Bajetta E, Gorbunova V, Bay JO, Bodrogi I, Jagiello-Gruszfeld A, Moore N: Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet* 2007;370:2103–2111.
- Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, Staroslawska E, Sosman J, McDermott D, Bodrogi I, Kovacevic Z, Lešovoy V, Schmidt-Wolf IG, Barbarash O, Gokmen E, O'Toole T, Lustgarten S, Moore L, Motzer RJ: Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 2007;356:2271–2281.
- Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, Grunwald V, Thompson JA, Figlin RA, Hollaender N, Urbanowitz G, Berg WJ, Kay A, Lebowitz D, Ravaud A: Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet* 2008;372:449–456.
- Tamaskar I, Garcia JA, Elson P, Wood L, Mekhail T, Dreicer R, Rini BI, Bukowski RM: Antitumor effects of sunitinib or sorafenib in patients with metastatic renal cell carcinoma who received prior antiangiogenic therapy. *J Urol* 2008;179:81–86, discussion 86.
- Richter S, Pfister D, Thüer D, Engelmann UH, Heidenreich A: Second-line treatment of progressive metastatic renal cell cancer with temsirolimus following first-line therapy with sunitinib or sorafenib (abstract V684). *Onkologie* 2008;31:234.
- Zimmermann K, Schmitt A, Steiner U, Asemussen AM, Knoedler M, Thiel E, Miller K, Keilholz U: Sunitinib treatment for patients with advanced clear-cell renal-cell carcinoma after progression on sorafenib. *Oncology* 2009;76:350–354.
- Shepard DR, Rini BI, Garcia JA, Hutson TE, Elson P, Gilligan T, Nemec C, Lopez R, Bornner D, Dreicer R, Bukowski RM: A multicenter prospective trial of sorafenib in patients (pts) with metastatic clear cell renal cell carcinoma (mccRCC) refractory to prior sunitinib or bevacizumab (abstract). *J Clin Oncol* 2008;26(suppl):5123.
- Choueiri TK, Brick AJ, McDermott D, Clement J, Kwabi C, Shah K, Chen K, Duh MS, Neary MP, Oh WK: Treatment and dosing patterns for angiogenesis inhibitor (AI) therapies in patients with metastatic renal cell carcinoma (mRCC) (abstract). *Ann Oncol* 2008;19:593.
- Heuer R, Eichelberg C, Zacharias M, Heinzer H: Sequential use of the tyrosine kinase inhibitors sorafenib and sunitinib. *J Urol* 2009;181(suppl 1):501.
- Dudek AZ, Zolnieriek J, Dham A, Lindgren BR, Szczylik C: Sequential therapy with sorafenib and sunitinib in renal cell carcinoma. *Cancer* 2009;115:61–67.
- Di Lorenzo G, Carteni G, Autorino R, Bruni G, Tudini M, Rizzo M, Aieta M, Gonnella A, Rescigno P, Perdoni S, Giannarini G, Pignata S, Longo N, Palmieri G, Imbimbo C, De Laurentis M, Mironi V, Ficorella C, De Placido S: Phase II study of sorafenib in patients with sunitinib-refractory metastatic renal cell cancer. *J Clin Oncol* 2009;27:4469–4474.
- Sablin MP, Negrier S, Ravaud A, Oudard S, Balleyguier C, Gautier J, Celier C, Medioni J, Escudier B: Sequential sorafenib and sunitinib for renal cell carcinoma. *J Urol* 2009;182:29–34, discussion 34.
- Garcia JA, Hutson TE, Elson P, Cowey CL, Gilligan T, Nemec C, Dreicer R, Bukowski RM, Rini BI: Sorafenib in patients with metastatic renal cell carcinoma refractory to either sunitinib or bevacizumab. *Cancer* 2010;116:5383–5390.
- Buchler T, Klapka R, Melichar B, Brabec P, Dusek L, Vyzula R, Abrahamova J: Sunitinib followed by sorafenib or vice versa for metastatic renal cell carcinoma – data from the Czech registry. *Ann Oncol* 2012;23:395–401.
- Herrmann E, Marschner N, Grimm MO, Ohlmann CH, Hutzschenreuter U, Overkamp F, Groschek M, Blumenstengel K, Puhse G, Steiner T: Sequential therapies with sorafenib and sunitinib in advanced or metastatic renal cell carcinoma. *World J Urol* 2011;29:361–366.
- Porta C, Procopio G, Carteni G, Sabbatini R, Bearz A, Chiappino I, Ruggeri EM, Re GL, Ricotta R, Zustovich F, Landi L, Calcagno A, Imarisio I, Verzoni E, Rizzo M, Paglino C, Guadalupi V, Bajetta E: Sequential use of sorafenib and sunitinib in advanced renal-cell carcinoma (RCC): an Italian multicentre retrospective analysis of 189 patient cases. *BJU Int* 2011;108(8 Pt 2):E250–E257.
- Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancy J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–247.
- R Development Core Team. R: A Language and Environment for Statistical Computing. Vienna, R Foundation for Statistical Computing, 2009 (<http://www.R-project.org>).
- Rufibach K: Reporttools: R functions to generate latex tables of descriptive statistics. *J Stat Soft* 2009;31:1–7.
- Ambring A, Stierner, U, Anders O, Björholt I: Sorafenib and sunitinib in renal cell cancer: a study based on register data (abstract). *J Clin Oncol* 2011;29:4600.

- 25 Rini BI, Escudier B, Tomczak P, Kaprin A, Szczyluk C, Hutson TE, Michaelson MD, Gorbunova VA, Gore ME, Rusakov IG, Negrier S, Ou YC, Castellano D, Lim HY, Uemura H, Tarazi J, Cella D, Chen C, Rosbrook B, Kim S, Motzer RJ: Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet* 2011;378:1931–1939.
- 26 Vickers MM, Choueiri TK, Rogers M, Percy A, Finch D, Zama I, Cheng T, North S, Knox JJ, Kollmannsberger C, McDermott DF, Rini BI, Heng DY: Clinical outcome in metastatic renal cell carcinoma patients after failure of initial vascular endothelial growth factor-targeted therapy. *Urology* 2010;76:430–434.
- 27 Busch J, Seidel C, Kempkensteffen C, Johannsen M, Wolff I, Hinz S, Magheli A, Miller K, Grunwald V, Weikert S: Sequence therapy in patients with metastatic renal cell carcinoma: comparison of common targeted treatment options following failure of receptor tyrosine kinase inhibitors. *Eur Urol* 2011;60:1163–1170.
- 28 Grunwald V, Seidel C, Fenner M, Ganzer A, Busch J, Weikert S: Treatment of everolimus-resistant metastatic renal cell carcinoma with VEGF-targeted therapies. *Br J Cancer* 2011;105:1635–1639.
- 29 Calvo E, Escudier B, Motzer RJ, Oudard S, Hutson TE, Porta C, Bracarda S, Grunwald V, Thompson JA, Ravaud A, Kim D, Panneerselvam A, Anak O, Figlin RA: Everolimus in metastatic renal cell carcinoma: subgroup analysis of patients with 1 or 2 previous vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapies enrolled in the phase III RECORD-1 study. *Eur J Cancer* 2012;48:333–339.
- 30 Porta C, Bellmunt J, Eisen T, Szczyluk C, Mulders P: Treating the individual: the need for a patient-focused approach to the management of renal cell carcinoma. *Cancer Treat Rev* 2010;36:16–23.
- 31 Escudier BJ, Bellmunt J, Negrier S, Melichar B, Bracarda S, Ravaud A, Golding S, Jethwa S: Final results of the phase III, randomized, double-blind AVOREN trial of first-line bevacizumab (BEV) + interferon- α 2a (IFN) in metastatic renal cell carcinoma (mRCC) (abstract). *J Clin Oncol* 2009;27(suppl):5020.
- 32 Porta C, Procopio G, Carteni G, Sabbatini R, Bearz A, Chiappino I, Ruggeri EM, Lo Re G, Ricotta R, Zustovich F: An Italian multicentre retrospective analysis of 189 advanced renal-cell carcinoma patients treated sequentially, either with sorafenib followed by sunitinib, or vice versa (abstract 922P). *Ann Oncol* 2010;21:viii289.